

**REMARKS*****Status of the Specification***

The specification has been amended so that "Tween 80" is recited in all-caps followed by its generic name as follows: TWEEN 80 (polysorbate 80).

No new matter has been added.

***Status of the Claims***

Claims 6, 11, 14, 18 and 41-47 are pending; claims 6, 11, 14 and 18 are currently amended; new claims 42-47 are added; and claims 1-5, 7-10, 12-13, 15-17 and 19-40 are canceled.

Claim 6 has been amended for improved grammar, and so that it recites the subject matter formerly recited in canceled claims 1-5, 37 and 38.

Claim 11 has been amended for improved grammar, so that it depends from claim 6 rather than canceled claim 7 and so that it recites the process steps formerly recited in canceled claim 7.

Claim 14 has been amended for improved grammar, so that it depends from claim 6 rather than canceled claim 1 and so that it recites the subject matter formerly recited in canceled claims 15 and 16.

Claim 18 has been amended so that it depends from claim 14 rather than canceled claim 17, and for improved grammar so that it recites TWEEN 80 (polysorbate 80).

New claim 42 is directed to a pharmaceutical composition comprising the paste according to claim 6 or 11. Support for this claim is found, for instance, at page 12, lines 23-24 of the specification.

New claims 43 and 44 are directed to the paste of claim 6 with a viscosity at 25°C of between 0.43 and 0.55 poise or 0.43 poise, respectively. Support for these claims is found, for instance, in the specification at page 25, lines 14-19.

New claim 45 is directed to the paste of claim 6 which comprises 8.4 to 35.2 g of squalane per about 0.66 g of BCG-CWS. Support for this claim appears, for instance, in the specification at page 26, lines 9-10.

New claims 46 and 47 are directed to the subject matter presented in claim 6, but edited for grammar.

No new matter has been added.

#### **1. Objections to the Specification**

The Examiner has objected to the specification for reciting the trademark, TWEEN 80, in lowercase letters and without referencing its generic name, polysorbate 80. (Office Action, page 3). Applicants have amended the specification as required by the Examiner, thereby overcoming the objection.

#### **2. Claim Objections**

The Examiner has objected to claims 6, 18 and 38 for informalities. (Office Action, page 3). As discussed above, Applicants have amended claim 6 to first recite, "Bacillus Calmette-Guerin – Cell Wall Skeleton," the full term for "BCG-CWS." Applicants have amended claim 18 so that TWEEN 80 is recited in all capital letters. Applicants have canceled claim 38. With these claim amendments and cancellations, Applicants have overcome all claim objections.

**3. Claim Rejections under 35 USC Section 112, Second Paragraph**

The Examiner has rejected claims 1 and 2 as allegedly indefinite for reciting 25°C in parentheses. (Office Action, page 4). Claims 1 and 2 have been canceled, and this limitation is now recited in claim 6 without parentheses, thereby obviating the rejection.

The Examiner has rejected claim 15 as allegedly indefinite for the reasons recited on page 4 of the Office Action. Although claim 15 has been canceled, the allegedly indefinite limitation of that claim is now recited in claim 14 with improved grammar which obviates the rejection.

**4. Claim Rejections under 35 USC Section 102**

The Examiner has rejected claim 1, 2, 4-6, 11, 14-19, 37, 39 and 41 as allegedly anticipated by Azuma et al. The Examiner's detailed reasoning for imposing this rejection appears on pages 5-7 of the Office Action, and is not reproduced here.

Applicants point out that claim 38 is not included in this rejection, which means that the Examiner recognizes the novelty of claim 38. As described above, Applicants have amended claim 6 so that it recites the limitation regarding the particles of the present invention having a single-peak particle size distribution, which was formerly recited in canceled claim 38. Accordingly, the anticipation rejection is overcome.

**5. Claim Rejections under 35 USC Section 103**

The Examiner has rejected claims 1, 2, 4-6, 11, 14-19, 37-39 and 41 as allegedly obvious over Azuma et al. in view of Van Nest et al. (Office Action, pages 7-12). Applicants respectfully traverse.

It is well settled that a *prima facie* case of obviousness is only established if all claim limitations are taught or suggested by the prior art, and there is some suggestion or motivation to combine the cited prior art references with a reasonable expectation of success, *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974) and *In re Vaeck*, 947F.2d 488, 493, 20 USPQ2d 1438, 1442

(Fed. Cir. 1991). Moreover, the teaching or suggestion to make the combination, together with the reasonable expectation of success, cannot be based on Applicants' own disclosure. *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991) (Emphasis added). In other words, it is impermissible to engage in hindsight reconstruction of the claimed invention, using the Applicants' invention as a template and selecting elements from references to fill the gaps. *In re Fritch*, 972 F.2d 1260, 1266, 23 USPQ2d 1780, 1784 (Fed. Cir. 1992).

To prevent such hindsight combinations, Federal Circuit case law "requires the Examiner to show a motivation to combine the references that creates the case of obviousness. In other words, the Examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the matter claimed." *In re Rouffet*, 47 USPQ2d 1453, 1457-1458 (Fed. Cir. 1998).

With these standards in mind, Applicants point out that the Van Nest reference discloses oil-in-water emulsions comprising muramyl dipeptide derivatives in which the particle size is 0.5-0.8 microns. Van Nest also teaches that reducing oil droplet size improves adjuvant performance. But the muramyl dipeptides taught by Van Nest have different physical properties from the BCG-CWS of the present invention. A person of ordinary skill in the art could, without difficulty, prepare emulsions comprising sub-micron droplets with the muramyl dipeptides and structure described in Van Nest. This is clearly taught in Van Nest, for example, at page 7, line 15:

*"The manner in which the droplet size of the invention is reached is not important to the practice of the present invention."*

In contrast, the active ingredient used in the present invention is an insoluble fraction of the cell wall of bacillus Calmette-Guerin (BCG) comprising large molecular weight substances with complicated structures, including mycolic acid, arabinose and muramyl dipeptide as illustrated in attached Appendix I.

Given that a person of ordinary skill in the art would recognize the significant and substantial differences in the physical properties between the muramyl dipeptides taught by Van Nest and the presently claimed BCG-CWS, the teachings of Van Nest are not informative to the preparation of the pastes of the present invention comprising BCG-CWS and squalane, which serve as the emulsion starting material. Van Nest gives no hints for solving the problem solved by the present invention.

Turning to the Azuma reference, it teaches the use of an organic solvent as a dispersion-aiding solvent for preparing a composition comprising BCG-CWS and oil. But the problem to be solved by the present invention is to prepare a composition comprising finer and more homogeneous particles than those described in Azuma. Azuma does not teach or suggest any specific methods to solve this problem and accomplish such a result. Furthermore, compare Figure 2 of the present specification to Figures 1-3 and 6-9 of Azuma; the present invention represents an approximate 6 to 10-fold reduction in average particle size to 0.4 to 0.5 microns from 3 to 4 microns. When a paste of the present invention is prepared using an organic solvent disclosed in Azuma reference, specifically, toluene or heptane, the average particle diameter is not less than 1 micron and goes beyond the limits of Claim 38. (See Fig. 2 of the present specification).

In view of the foregoing points and discussion, Applicants submit that any determination of obviousness based on the cited references necessarily involves the use of Applicants' own disclosure as a template because the teachings of the cited prior art references provide no reasonable expectation of successfully inventing the presently claimed emulsions and pastes, in violation of the Federal Circuit's strong prohibition against the use of hindsight in an obviousness analysis. The Examiner has therefore failed to establish *prima facie* obviousness.

Moreover, the present inventors have succeeded in obtaining surprisingly advantageous particles of an extremely homogeneous and fine quality, as shown in Figs. 1, 2 and Table 10 of the specification, by using a mixed solvent of a hydrocarbon and ethanol, e.g. claim 11. (Compare Figure 1 which shows particle diameter of heptane only BCG-CWS emulsions (as in Azuma) and Figure 2 which shows particle diameter of mixed heptane/ethanol BCG-CWS emulsions.

For at least the foregoing reasons, Applicants submit that the presently claimed pastes are nonobvious over the prior art cited by the Examiner. Applicants respectfully request reconsideration and withdrawal of the obviousness rejection.

**6. Conclusion**

In view of the foregoing amendments and remarks, Applicants respectfully request allowance of the application, the claims of which define subject matter that meets all statutory patentability requirements.

Pursuant to 37 C.F.R. §§ 1.17 and 1.136(a), Applicants respectfully petition for a one (1) month extension of time for filing a reply in connection with the present application, and the required fee is attached hereto.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Mark J. Nuell, Reg. No. 36,623 at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.14; particularly, extension of time fees.

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Respectfully submitted,

By Mark J. Nuell

Mark J. Nuell  
Registration No.: 36,623  
BIRCH, STEWART, KOLASCH & BIRCH, LLP  
12770 High Bluff Drive  
Suite 260  
San Diego, California 92130  
(858) 792-8855  
Attorney for Applicant